REMARKS

This is responsive to the Office Action mailed March 24, 2005.

Claims 8 and 79-85 were previously pending in this application. By this amendment, Applicant is canceling claim 80 without prejudice or disclaimer. Claim 8 has been amended. Support for the "fragment of SEQ ID NO:2" limitation is found in claim 80 and in the specification, e.g., on page 16, lines 10-12 and on page 1, line 9. Support for the "presentation by antigen presenting cells" limitation is found in the specification, e.g., on page 4, lines 5-10, on page 1, lines 9-10 and on page 16, lines 2-4. As a result, claims 8, 79, and 81-85 are now pending for examination with claim 8 being independent claim. No new matter has been added.

Request to Withdraw the Finality of the Office Action

Applicant respectfully requests withdrawal of the finality of the Office Action. The present written description rejection of claims 8 and 79-85 appears to be a new rejection not necessitated by Applicant's previous amendment.

In the response to the previous Office Action, Applicant removed language relating to functional variants from the claims. The present written description rejection objects to the same claims based on the claimed peptides not necessarily being a subsequence of MAGE-A1. This aspect of the claims was not amended, and therefore Applicant's previous amendment of the claims cannot have caused the rejection. Thus, the finality of the Office Action appears to be improper, and Applicant respectfully requests its withdrawal

Rejection Under 35 U.S.C. § 112, First Paragraph

Written Description Rejection

The Examiner rejected claims 8 and 79-85 as lacking an adequate written description. Applicant respectfully requests reconsideration.

Applicant has amended claim 8 to limit the peptides used in the claimed methods to fragments of SEQ ID NO:2, i.e., subsequences of SEQ ID NO:2, that include SEQ ID NO:10.

Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 8 and 79-85 under 35 U.S.C. 112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 8 and 79-85 as indefinite for the use of the term "the complex" in the last line of the claim. Applicant respectfully requests reconsideration.

Applicant has amended claim 8 to remove this term, thereby rendering this rejection moot. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claims 8 and 79-85 under 35 U.S.C. 103(a) as unpatentable over US 6,667,037 in view of WO 95/04542, Rammensee, et al., (Immunogenetics, 1995, 41: 178-228), Rammensee, et al., (MHC Ligands and Peptide Motifs, 1997, pages 263-265) and prior art on pages 62-63 of the specification that describes the frequency of HLA-B35 in the population.

The Examiner stated that US 6,667,037 discloses some of the peptides recited in the claims (SEQ ID NOs: 8 and 10). The Examiner also stated that US 6,667,037 discloses the use of tyrosinase peptides to induce an immune response in HLA-B35 positive patients. Further, the Examiner stated that US 6,667,037 discloses that it is known that individuals express six HLA molecules on cell surfaces. The particular example cited is a CTL that recognizes tyrosinase peptides presented by a target cell that expresses HLA molecules A24, B35, B44 and Cw*04.

The Examiner admits that US 6,667,037 does not disclose the administration of the instantly claimed peptides from MAGE-A1 to a HLA-B35 positive subject to induce a specific immune response. (page 4 of Office Action)

Thus, all that US 6,667,037 discloses with respect to the claimed peptides is that SEQ ID NO:8 is a peptide derived from MAGE-1. US 6,667,037 does not disclose the ability of this peptide to specifically stimulate an immune response via its presentation by HLA-B35. Any references combined with US 6,667,037 must, therefore, teach this aspect of the claimed invention that is missing from US 6,667,037.

The Examiner asserts that several references supply the limitations missing from US 6,667,037. In particular, the Examiner asserts that WO 95/04542 teaches that MAGE-1 is a tumor rejection antigen precursor (TRAP) that contains peptides that are tumor rejection antigens (TRAs). The Examiner further asserts that TRAs from one region of a TRAP can be combined with peptides having a different MHC restriction in order to broaden the immunological coverage of a composition (see page 4 of Office Action, fourth paragraph).

This general disclosure in WO 95/04542 does not supply the elements of the claimed invention that are missing from US 6,667,037, i.e., that SEQ ID NO:10 and related peptides are presented by HLA-B35.

The Examiner next cited two Rammensee articles that describe HLA-B35 motifs. According to the Examiner, the Rammensee Immunogenetics article teaches (1) that the HLA-

B35 motif includes anchor residues of proline at position 2 and tyrosine at position 9, and (2) that the peptide EADPTGHSY is a HLA-A1 T cell epitope.

The full set of anchor and "preferred residues" does not include the following residues (in bold + underline) of the EADPTGHSY peptide: **E**A**D**PT**GHS**Y. Thus, of the nine amino acids in the EADPTGHSY sequence, five are neither anchor nor preferred residues, three are preferred residues, and only one is an anchor residue.

Thus the Rammensee Immunogenetics article does not teach the use of EADPTGHSY (SEQ ID NO:8) and other claimed peptides for inducing an HLA-B35 restricted immune response with sufficient specificity to support the rejection, because the article teaches that the peptide is lacking one of two anchor residues, has only three preferred residues and further teaches that the peptide is an HLA-A1 binding peptide. Based on the Rammensee Immunogenetics teaching, one of ordinary skill in the art in reading this would have neither motivation to investigate (and even more so, to use) the claimed peptides as HLA-B35 binding peptides nor a reasonable expectation of success in doing so.

According to the Examiner, the Rammensee MHC Ligand and Peptide Motifs article teaches that HLA-B3501 binding peptides preferentially have alanine at position 2, proline at position 4, and threonine at position 5. Applicant wishes to call to the Examiner's attention that the HLA-B35 motif in the Rammensee MHC Ligands paper is identical to that of the Rammensee Immunogenetics paper. Further, while A is one of the "other preferred residues", it is not an anchor residue at P2 for HLA-B35.

While the A_2, P_4 and T_5 "preferred" amino acids match the sequence of the claimed peptides, Applicant notes that none of these residues is an anchor residue. Moreover, there are other amino acid residues also taught to be preferred at these positions for HLA-B35 binding. Specifically, there are 6 possible "preferred" or anchor residues at position 2, 5 possible "preferred" residues at position 4, and 8 possible "preferred" residues at position 5. Just for these three residues, the three amino acids are one of 240 possible sets (6 X 5 X 8). Considering the whole peptide sequence, and considering that none of the other 5 amino acids are "anchor" or

"preferred" residues, the sequence of EADPTGHSY is one of 6,400,000 possible sequences having A2, P4, T5 and Y9 (20 X 1 X 20 X 1 X 1 X 20 X 20 X 20 X 1), or only one of 768,000,000 possible sequences (20 X 6 X 20 X 5 X 8 X 20 X 20 X 20 X 1).

Taking the further teachings of Rammensee that EADPTGHSY is a HLA-A1 binding peptide, and that the HIV env peptide TAVPWNASW is a HLA-B35 peptide, one of ordinary skill in the art would not be led to conclude that EADPTGHSY would bind HLA-B35 (if not led away from this), because (1) Rammensee does not teach that the peptide does bind HLA-B35, but implicitly teaches that it does not bind HLA-B35, and (2) the claimed peptide and the HIV env peptide share only 3 of 9 amino acid residues (P2, P4, and P8).

The Examiner also indicates that the fact that the HIV env peptide has non-preferred residues at certain of the P2, P4, P5 and P9 residues supports the argument. On the contrary, accepting non-preferred residues at these positions would expand the possible genus of HLA-B35 binding peptides and thus make it less likely that one of ordinary skill in the art would pick EADPTGHSY as a HLA-B35 binding peptide.

Moreover, there is no reason that one of ordinary skill in the art would select the specific preferred amino acids selected by the Examiner in rejecting the claims. The Examiner appears to be picking and choosing from the lists of preferred residues for positions 2, 4 and 5 of Rammensee, based solely on hindsight knowledge of Applicant's results with this peptide (and with even more hindsight from among non-preferred residues). No other basis for selecting the specific residues found in Applicant's peptide is offered by the Examiner.

The Examiner also cited the Pagupathi reference from Applicant's specification as teaching the frequency of HLA-B35 alleles in the population. It is not clear why this reference is cited as the Office Action makes no further reference to it or its teachings in the claim rejection.

In combining the references, the Examiner appears to suggest (page 5 of the Office Action, third paragraph) that one of ordinary skill in the art would combine the references in order to add the EADPTGHSY peptide to a HLA-B35 directed composition because US

6,667,037 teaches that combining tyrosinase peptides with peptides from other TRAPs such as MAGE-1 and because WO 95/04542 teaches that peptides from one region of a TRAP can be combined with peptides having different MHC restriction properties.

This reasoning does not make out a prima facie case of obviousness for the following reasons. First, Applicant's claims do not combine peptides. Thus it is not clear why combining the references in such a way that a combination of peptide is achieved would render the claimed invention obvious.

Second, the teachings of US 6,667,037 and WO 95/04542 are contrary, and thus the combination of these does not support a prima facie case of obviousness. US 6,667,037 teaches combining peptides from different TRAPs, whereas WO 95/04542 teaches using peptides from different regions of a TRAP. Neither of these combinations is claimed by Applicant.

Third, the Examiner states that the motivation to combine the cited references is that one of ordinary skill in the art would do so to make a composition that contained both HLA-B35 binding peptides and HLA-A1 binding peptides. The Examiner extrapolates the teachings of Rammensee regarding peptide motifs to assert that the use of the MAGE-A1 peptide claimed for use by Applicant would have been obvious.

Applicant respectfully disagrees that one of ordinary skill in the art would be motivated to select and use the specific peptide as claimed by Applicant. In addition, Applicant respectfully disagrees that one of ordinary skill in the art would have had a reasonable expectation of success in using the claimed peptide for stimulating immune responses in HLA-B35 positive individuals, based on the existence of a mere motif, which does not fit the claimed peptide well, particularly in view of the conflicting motif taught by Rammensee as described above.

The Examiner stated that "[i]t is an expected property of the EADPTGHSY peptide that it would stimulate an ... immune response in an HLA-B35 positive subject who also was positive for HLA-A1, the immune response being restricted to either HLA-A1 and/or HLA-B35." Office

Action, page 6, second paragraph. Applicant respectfully disagrees. While one of ordinary skill in the art could reasonably expect that the EADPTGHSY peptide would stimulate an HLA-A1 restricted immune response, there is absolutely nothing in the art that would have provided one of ordinary skill in the art with a reasonable expectation of success that this peptide would stimulate an HLA-B35 restricted immune response, given that there were no teachings in the art of HLA-B35 binding by EADPTGHSY.

In fact, the Examiner has not presented any reason why one of ordinary skill in the art would have looked for HLA-B35 binding or presentation, because as shown above, the claimed peptide is one of many thousands or millions of peptides that could match the HLA-B35 motif sequence as reported by Rammensee. The Examiner has not cited any reference that would provide motivation to one of ordinary skill in the art to test SEQ ID NO:10 in particular as a HLA-B35 binding peptide. That motivation is essential to a *prima facie* case of obviousness.

The Examiner also stated that, because US 6,667,037 teaches the use of only one CTL restricted to one HLA molecule, "one of ordinary skill in the art at the time the invention was made would have realized that only one CTL was tested and that that did not preclude that other peptides from other proteins could be presented by HLA molecules." Office Action at page 7.

Such a statement does not represent a legally sufficient reason to reject the claims as obvious. Even if the statement is correct, the fact that something is not precluded does not mean that it is obvious to one of ordinary skill in the art, in this case because there is no reasonable expectation that the peptide would function as now demonstrated and claimed by Applicant.

While not making Applicant's claims obvious, the objection raised by the Examiner might be better classified as a suggestion that the claims methods are "obvious to try", which is not a proper and legitimate standard for unpatentability, and does not constitute obviousness. In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988); In re Fine, 837 F.2d 1071 (Fed. Cir. 1988). See also In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). However, even the suggestion that the claimed invention is obvious to try does not have a sufficient basis, because there is nothing

in the cited references that directs one of ordinary skill in the art to try the specific MAGE polypeptides in the claimed methods.

Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 8 and 79-85 under 35 U.S.C. 103.

Conclusion

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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